983,848

PATENT SPECIFICATION

DRAWINGS ATTACHED

983,848

Date of Application and filing Complete Specification: March 9, 1961.

No. 8667/61.

Application made in Netherlands (No. 249,361) on March 12, 1960.

Complete Specification Published: Feb. 17, 1965.

Index at acceptance:—C2 C(2A3, 2B2A4, 2B2G5, 2B2J, 2B21, 2T16, 3A7V1A4, 3A7V1E2, 3A7V1F2, 3A7V1G2, 3A7V1J1, 3A7V2A1, 3A7V2A4, 3A7V2E1, 3A7V2F1, 3A7V2G1, 3A7V2G2, 3A7V2K2, 3A7V2K4, 3A8A4, 3A8B2, 3A8C1, 3A8J, 3A10E3A4, 3A10E3B4, 3A10E3C4, 3A10E3D1, 3A10E4A4, 3A10E4B1, 3A10E5A, 3A10E5E, 3A13A3A4, 3A13A3B1, 3A13A3B2, 3A13A3C, 3A13A3H2, 3A13C1C, 3A13C3C, 3A13C6C, 3A13C9, 3A13C10F, 3A13C10H, 3A13D, 3C10)

Int. Cl.:—C 07 d

COMPLETE SPECIFICATION

Improvements in or relating to Indoloquinolizine Compounds

We, N.V. PHILIPS' GLOEILAMPENFABRIEKEN, a limited liability Company, organized and established under the laws of the Kingdom of the Netherlands, of Emmasingel 29, Eindhoven, Holland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to indoloquinolizines and is concerned with certain novel compounds of this class having pharmacological applications. The ensuing description refers to the accompanying drawings in which are set out certain structural chemical formulae, serially numbered.

It is known that the Rauwolfia - alkaloid reserpine has a number of important pharmacological properties, so that this substance has been used for medical purposes both as a blood-pressure reducing means and as a sedative.

After it came to be known that reserpine is a compound of the Formula I wherein R_1—R_3 are methoxy groups, several efforts have been made to find reserpine analogoes having either the sedative or the blood-pressure reducing activity of reserpine, but not both at the same time, since when using a sedative the blood-pressure decreasing activity is generally not desired and when using a blood-pressure reducing means the central activity is generally not desired.

Thus, groups of compounds of the Formula I have been described which differ from reserpine only in the radicals R_1—R_3. One of these groups has substantially the central-depressing action of reserpine with a small effect upon blood-pressure and another group has substantially the hypotensive activity and, in addition, a central action much weaker than that of reserpine.

Experiments have also been made for the purpose of simplifying the structure of reserpine in compounds which still retained the pharmacological activity of reserpine. Thus, compounds of the Formula II have been described and claimed in British Patent Specification No. 841,225, in which formula R_1 is a hydrogen atom or an acyl group, R_2 is a hydrogen atom or an alkyl group, and R_3 and R_4 are hydrogen or halogen atoms or etherified or esterified hydroxyl groups, which compounds have both the blood-pressure reducing and the central depressing activity of reserpine.

Compounds of a simplified reserpine structure which exhibit one of the two said properties of reserpine and not the other or to a very small extent only, have not been described hitherto.

According to the present invention there are provided compounds of the Formula III or acid-addition salts thereof, wherein Y is a free, etherified or esterified hydroxyl group and $n^1=0$, 1 or 2, X is a free or esterified hydroxyl group, or a —C≡N group, or a carboxyl group esterified by an aliphatic alcohol with 1 to 4 carbon atoms, and n=0—4. These compounds have an action upon the central nervous system similar to reserpine, but have substantially no influence upon blood-pressure. They can be used therapeutically as sedatives with reserpine activity without hypotensive additional action, whilst such compounds can be manufactured in a simpler manner than

[*Price 4s. 6d.*]

reserpine and reserpine analogues having a substantially sedative activity.

The invention further includes processes which will be described below for the preparation of these compounds and also pharmaceutical preparations comprising the same as active ingredients which will also be described hereinafter.

Compounds according to the invention may be administered to mammalia in doses of from 1 to 200 mg/kg 3 to 5 times per day to obtain a reserpine-like central-depressing activity. They may be worked up in known manners into pharmaceutical preparations by mixing them with, or dissolving or dispersing them in, solid or liquid carriers.

The activity of the compounds was determined in tests with mammalia.

For example, after interperitoneal administration of doses from 10 to 100 mg/kg to mice, the animals were found to be strongly sedated shortly after the administration, which became clearly manifest more particularly with the ptosis occurring.

The sedating action clearly appeared also from a potentiation of other central depressives.

This potentiation was measured in two ways:

Firstly, it was examined to what extent the Nembutal narcosis, ("Nembutal" is a Registered Trade Mark), that is, the narcosis after administration of a preparation of 5 - ethyl - 5 - (1^1 - methylbutyl) barbituric acid, was lengthened by a previous treatment with compounds within the invention. The results of these tests, as carried out for example with two compounds within the invention, are summarized in Table I. In that Table, the abbreviation "i.p." denotes administration by interperitoneal injection.

TABLE I

Substance	animal sex	animal number	dose mg/kg i.p.	period of the previous treatment in minutes	duration of narcosis in minutes
Control	♂	60	—	—	33.2
Control	♀	60	—	—	31.3
Cria 1	♂	10	50	30	186
Cria 1	♂	10	50	60	98
Cria 1	♂	10	50	120	48.5
Cria 204	♀	10	100	30	186.5
Cria 204	♀	10	100	60	2.205
Cria 204	♀	9	100	120	186

The duration of the narcosis with mice each weighing from 15 to 20 gms was measured after interperitoneal administration of 50 mgms/kg of "Nembutal." In the tests, sedative was not previously administered. The compounds designated Cria 1 and Cria 204 are substances of the Formula III, wherein respectively $n^1=0$, $n=1$ and $X=OH$; and $n^1=0$, $n=1$ and X is a 3,4,5 - trimethoxybenzoyloxy group as represented by Formula XIV which substances were administered, prior to the injection with "Nembutal," in doses indicated in column 4, to numbers of mice indicated in column 3, for a number of minutes indicated in column 5.

In another method, the potentiation of narcosis by administration of compounds within the invention was measured by testing during a previous treatment with what dose of the substance to be tested a normally non-narcotic dose of intravenously - administered hexobarbital (a preparation of 5 - ($\Delta^{1.2}$ - cyclohexenyl) - 5 - methyl - N - methylbarbituric acid) does bring about narcosis.

The substance to be tested was interperitoneally administered to a number of mice half an hour before the administration of hexobarbital and that dose of the substance to be tested was measured which was sufficient to bring abour narcosis with 50% of the animals: that dose is designated the E.D.50 of the substance tested. These doses were found to be

for Cria 1	40.8 mgs/kg
for Cria 204	12.2 mgs/kg
for Crip 207	3.5 mgs/kg

Crip 207 is a compound of the Formula III,

wherein n=2 and n^1=0 and X=—C≡N.

The tranquilizing activity of compounds was measured by the suppression of the fighting tendency of two mice which were subjected to an electroshock through their legs. In these tests, for example, after interperitoneal administration of Cria 1 and Cria 204 half an hour before the test there were found E.D.50's of 50.1 mgms/kg and 5.1 mgms/kg respectively, that is to say that with these doses the fighting tendency was suppressed with exactly 50% of the animals tested. The absence of the blood-pressure reducing action was determined, for example, by measuring the blood-pressure of a cat narcotized with chloralose upon administration of Cria 1.

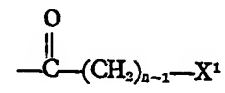
With doses up to 2 mgms/kg no influence upon blood-pressure could be found. With higher doses up to 8 mgms/kg only a small decline in blood-pressure occurred.

Compounds according to the invention may be manufactured by processes analogous to those known for the manufacture of analogous compounds. The invention includes certain such processes, as will be further described below.

Known processes for building up the four-ring system of the Formula IV which may be used in preparing compounds according to the present invention, comprise three groups of processes which will be described, designated methods I, II, and III.

In method I beta - carboline derivatives constitute the starting material which thus already contains the three-ring system ABC, substituents being present in the ring C at the 1- and the 2-positions of the carboline skeleton, which may be cyclized to form ring D.

Thus, in practising the invention, a compound may be used as starting material corresponding to the general Formula V or a salt thereof, wherein R_1 is an alkyl group with 1 to 4 carbon atoms and X^1 represents X or an equivalent, that is to say, a group which can readily be converted into the group X by a known reaction subsequently without affecting the rest of the molecule. The substituents are cyclized into the ring D by means of a Dieckmann condensation, whereupon a compound with the four-ring system of Formula IV may be isolated having a keto group at the 2 - position and substituted by a



group at the 3 - position. The 2 - keto group may then be reduced to a methylene group, and if desired the carbonyl group in the 3 - substituent also reduced to a methylene group, and, if necessary, conversion is effected of the group X^1 into a group X.

For example a 1 - carbethoxymethyl - 1,2,3,4, tetrahydro - beta - carboline is converted by heating with the aid of an unsaturated aliphatic acid ester of a lower aliphatic alcohol (1—4 carbon atoms), for example the ethyl ester of acrylic acid, into a compound of the Formula VI or a salt thereof, which compound is cyclized by means of a Dieckmann condensation into a mixture of two compounds with a four-ring system of Formula IV, which compounds carry a keto group at the 2 - position and are substituted by a carbethoxy group respectively at the 1- and the 3-positions.

The last - mentioned 3 - carbethoxy compound is isolated from the mixture and, subsequently, the keto group at the 2 - position is converted by known processes into a methylene group. Such conversion may be effected, for example, by catalytic reduction, for example with the aid of Pt/H_2, followed by a treatment with phosphorus and hydriodic acid.

The carbethoxy group at the 3 - position may be converted, for example by reduction with the aid of a metal hydride or a metal - alkyl hydride into a carbinol group which is etherified or esterified, if desired, by known processes. The esterified carbinol group may be converted by treatment with KCN into a $—CH_2—C≡N$ group. It is also possible by known methods to lengthen this side-chain at the 3 - position to form a chain $—(CH_2)_n—X$, wherein n> 1. The carbinol group, for example, may be converted into a halogeno - methyl group which is subsequently converted into a Grignard compound which in turn is reacted with CO_2 to introduce a carboxyl group which may be esterified if desired with a lower aliphatic alcohol (1—4 carbon atoms) or reduced so that the original carbinol group is converted to a hydroxy - ethyl group. Thus, the substituent at the 3 - position has been lengthened by a methylene group.

The Dieckmann cyclization reaction may be carried out, for example, by heating the compound of Formula V in an inert solvent, for example in petroleum ether or dry benzene or toluene, in the presence of an alkali metal alkoxide, for example sodium methoxide.

In method II, the four-ring skeleton is built up by cyclizing a compound of the Formula VII or a salt thereof, in a Bischler-Napieralsky reaction into a compound of the Formula VIII wherein R_2 represents $—(CH_2)_n—X$, n being zero to 4 or an equivalent as hereinbefore defined and Z^- is an anion of an acid, preferably an inorganic acid, for example hydrochloric acid, sulphuric acid or perchloric acid.

Reducing the double bond in the D-ring of the compound of Formula VIII yields a compound having the skeleton of Formula IV. The Bischler - Napieralsky reaction is carried out in known manner by boiling the compound of Formula VII in an inert solvent, preferably benzene or toluene, with $POCl_3$. After

decanting the cooled solution into a cold aqueous solution of a strong acid, the salt of Formula VIII is obtained.

The reduction of the 5—12b double bond in the compound of Formula VIII for obtaining a compound having the skeleton of Formula IV may be effected by methods known for such reductions, for example with an alkali metal or alkaline - earth metal and an alcohol, by catalytic hydrogenation, for example with Pt/H_2 or with zinc and $HClO_4$, or with a metal hydride or a metal - alkyl hydride, for example $LiAlH_4$ or di - isobutylaluminium hydride.

Very good yields may be obtained by reducing the compound of Formula VIII in solution in tetrahydrofurane or petroleum ether with the aid of a metal hydride or a metal - alkyl hydride, for example $LiAlH_4$ or di - isobutylaluminium hydride.

Compounds corresponding to Formula VII are obtained, for example, by alkylating a tryptamine, which may be substituted in the benzene ring, or a salt thereof, with a compound of Formula IX wherein R_3 is an alkoxyl group with 1 to 4 carbon atoms, R_2 represents $-(CH_2)_n-X$ or a group convertible thereto, n being zero to four and R_4 is a halogen atom, preferably a chlorine atom or a bromine atom, in which event $n^{11}=2$, or a double-bonded oxygen atom, in which event $n^{11}=1$.

The secondary amine is cyclized by heating into a compound corresponding to Formula VII.

A reductive alkylation of a tryptamine, which may be substituted in the benzene ring, is carried out, for example, with the alpha-aldehydo-glutaric diethyl ester. This compound is obtained in the enol state by reaction of the diethyl glutarate with ethyl formate.

This alkylating reaction may be carried out in two steps, in that firstly the enamine of Formula X is obtained, which is converted by catalytic reduction, followed by cyclization, into a compound corresponding to Formula VII.

Compounds of Formula VII may also be manufactured, for example, by reaction of a tryptyl halide which may be substituted in the benzene ring, with a piperidine derivative of Formula XI wherein R_2 represents $-(CH_2)_n-X$, n being zero to 4, or a group convertible thereto.

In method III, the rings A and B are built up on a compound already containing the rings C and D of the skeleton of Formula IV by means of a Fischer indole synthesis.

A compound of Formula XII or a salt thereof, wherein $R_2=-(CH_2)_n-X$, n being zero to four, or an equivalent as defined above, is caused to react with a phenylhydrazine, which may be substituted in the benzene ring, for manufacturing a compound corresponding to Formula XIII. This reaction may be carried out in the manners known for manufacturing phenylhydrazones, for example by boiling the mixture of the compound of Formula XII and the phenylhydrazine in a solvent. Very satisfactory yields were obtained by using as a solvent a mixture of glacial acetic acid and ethanol, cooling the mixture after boiling for about half an hour, dissolving the reaction mixture in ether and, subsequently, adding a strong inorganic acid, for example perchloric acid, whereupon the salt of the compound corresponding to Formula XIII crystallizes. The ring B of the skeleton of Formula IV is subsequently formed by cyclizing the compound of Formula XIII in a manner known for the Fischer indole synthesis, for example by dissolving the compound of Formula XIII in ethanol, passing hydrogen chloride gas through the solution until saturation, and leaving the mixture saturated with hydrogen chloride to stand at room temperature for 10 to 20 hours. After the addition of ether, the hydrochloride of a compound having the skeleton of Formula IV crystallizes, which product is a compound of Formula III or a compound which is converted thereto by conversion of the group R_2 into a group $-(CH_2)_n-X$, if it is not already such group.

The invention is further illustrated in the ensuing specific examples wherein a number of embodiments of the process are described in more detail. In the examples percentages, unless otherwise specified, are weight for weight, and temperatures are in degrees centigrade.

Example I

3 - hydroxymethyl - 1,2,3,4,6,7,12,12b - octahydroindolo(2,3 a) - quinolizine.

A) Manufacture of α - oxymethylene - glutaric diethyl ester.

28 gms. (1.22 gm. atoms) of Na and 800 mls. of absolute toluene were introduced into a three-necked 5 litre flask with two branch tubes, provided with a vibrating stirrer, a thermometer, a dropping funnel, and a reflux condenser closed by a drying tube filled with KOH. The assembly was placed in an oil bath and boiled for some minutes while stirring. Subsequently, the oil bath was removed and the stirring process discontinued after cooling below the melting point of sodium (97.5°). Subsequently, a mixture consisting of 200 gms. (1.06 mol.) of diethyl glutarate and 124 gms. (1.68 mol.) of ethyl formate was added dropwise during 1.5 hours while cooling in ice and stirring. The stirring process was continued for another 20 hours, initially while cooling in ice, but for the last 10 hours at room temperature. The product, a yellow jelly-like mass, was poured into 2 litres of water containing 1 kgm of ice. The toluene layer was separated and washed with water. The aqueous layer and washings were bulked and washed twice with ether. Subsequently, the remaining aqueous layer, now pale yellow,

was acidified with 80% phosphoric acid and the resulting oil separated off. The aqueous layer was shaken another four times with 250 mls. portions of ether and these ether layers were added to the separated oil, and the ethereal solution was washed once more with a little water. After drying over $MgSO_4$ and distilling off the ether, the residue was distilled *in vacuo* through a Vigreux - fractionating column of 10 ccs. The following fractions were obtained:

1) 11 gms. having a boiling point up to 105°/0.8 mm Hg (temperature of the bath up to 145°), n_D^{20} 1.4410.

2) 106 gms. having a boiling point up to 105° to 107°/0.8 mm (temperature of the bath up to 145°), n_D^{20} 1.4502. Yield 46%.

3) 13 gms. having a boiling point of 107° to 115°/0.8 mm (temperature of the bath 145—200°), n_D^{20} 1.4495. Yield 6%.

Analysis of fraction 2: found C 55.3; H 7.3 $C_{10}H_{16}O_5$ (216.24): calculated C 55.54; H 7.46.

The compound was for the greater part or wholly in the enol state. The infra-red absorption spectrum showed a broad OH-band at 2500—3500 cm^{-1} and a C=C band at 1660 cm^{-1}.

The index of refraction n_D^{20} increased to 1.4551 after some weeks and thereafter remained substantially constant. Redistillation produced an index of refraction n_D^{20} 1.4504. The variation in the index of refraction was not accompanied by a noticeable variation in the infra-red absorption spectrum.

B) Coupling of tryptamine with α - oxymethylene - glutaric diethy ester.

24.0 gms. (0.15 mol.) of tryptamine dissolved in 150 mls. of absolute alcohol were dripped during 15 minutes into 32.4 gms. (0.15 mol.) of α - oxy - methylene - glutaric diethyl ester with stirring and cooling with ice and in an atmosphere of nitrogen. After stirring for another hour at room temperature, the mixture was boiled under reflux for 45 minutes, and the alcohol then removed *in vacuo*. The residue was dissolved in ether and the resulting solution washed successively with 0.1 N hydrochloric acid, saturated $NaHCO_3$-solution, and water. After drying over $MgSO_4$ and distilling off the ether, the residue was distilled in high-vacuum over some pieces of anthracite.

This yielded the following fractions:

1) 2.6 gms. boiling point up to 215°/0.05 mm. temperature of the bath up to 230°, enol positive.

2) 24.6 gms. (0.069 mol. or 46%), boiling point 215° to 220°/0.05 mm. temperature of the bath 230°; viscous.

3) 2.2 gms. boiling point 220°/0.05 mm. temperature of the bath 230° to 280°; vitreous. Residue 17 gms.

Analysis of fraction 2: found C 66.9, 66.6; H 7.3, 7.2; N 7.8, 7.8 $C_{20}H_{26}N_2O_4$ (358.42): calculated C 67.02 H 7.31 N 7.81.

C) Reduction of α - [2 - (3 - indolyl) - ethylaminomethylene] - glutaric diethyl ester.

24.6 gms. (0.069 mol.) of enamine, obtained by B), dissolved in 150 mls. of glacial acetic acid, was reduced at room temperature at a slight pressure above atmospheric pressure. PtO_2 as a catalyst was added in four portions each of 200 mgms. before and during reduction. The calculated amount of hydrogen was absorbed after 21 hours. The platinum was now filtered off and the acetic acid distilled off *in vacuo* with the temperature rising slowly, and eventually the temperature of the bath was maintained at 100° for another half an hour. The residue was dissolved in benzene and subsequently shaken successively with 1 N hydrochloric acid, saturated $NaHCO_3$-solution and water. The resulting washed benzene solution was dried over $MgSO_4$, the solvent distilled off and the residue distilled under high vacuum. This yielded, substantially without distillation residue, 16.8 gms. of a vitreous mass with boiling point 220°/0.01 mm. From this could be obtained, by recrystallizing several times from benzene - petroleum ether (60°—80°), 8.0 gms. (0.025 mol. or 36%) of a solid substance with melting point of 106° to 108° which was (1 - [2¹(3¹¹ - indolyl)ethyl]5 - carbethoxy - α - piperidone - 2).

Analysis: found C 68.3 H 6.9 N 8.9 $C_{18}H_{22}N_2O_3$ (314.37) calculated: C 68.77 H 7.1 N 8.9.

D) Bischler - Napieralsky ring closure.

7.2 gms. (0.023 mol.) of the substance obtained by C) was added in an atmosphere of nitrogen to 120 mls. of absolute benzene and 12 mls. of $POCl_3$. After standing for 15 minutes, the mixture was boiled under reflux in an atmosphere of nitrogen. Subsequently, the mixture was poured into 300 gms. of ice and 25 mls. of 70% $HClO_4$. The product, a yellow solid substance, was filtered off and washed with a little water. The yield was 8.4 gms. of 3 - carbethoxy - 1,2,3,4,6,7,12 - heptahydro - indolo (2,3 a) - quinolizinium perchlorate (0.021 mol. or 91%) with melting point 154° to 156°. After recrystallization from alcohol-water, the melting point increased to 156° to 158°.

Analysis: found C 54.5; H 5.4; N 6.9, 6.8; Cl 8.9, 9.1 $C_{18}H_{21}N_2O_6Cl$ (396.82) calculated C 54.48; H 5.33; N 7.06; Cl 8.94.

E) Reduction of the perchlorate obtained by D) with $LiAlH_4$.

A suspension of 5.0 gms. (0.013 mol.) of the compound obtained by D) in 350 mls. of absolute tetrahydrofurane was dripped during

15 minutes in an atmosphere of nitrogen, into a solution of 2.8 gms. (0.074 mol.) of $LiAlH_4$ in 260 mls. of absolute tetrahydrofurane. The resulting red solution was stirred for 15 minutes at room temperature and subsequently boiled under reflux. After 30 minutes the solution, which was now substantially colourless was decomposed in an ice-bath with 10 mls. of water, and the solid matter filtered off and washed on the filter with altogether 1 litre of tetrahydrofurane. The solutions of tetrahydrofurane were bulked and acidified with 11 mls. of 2 N hydrochloric acid. Next day the product was filtered off, which yielded after drying 3.51 gms. (0.012 mol. or 92%) of pure HCl - salt of 3 - hydroxy - methyl 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine.

Analysis: found C 65.7; H 7.4; N 9.4; Cl 12.1 $C_{16}H_{21}N_2OCl$ (292.80) calculated: C 65.63; H 7.23; N 9.57; Cl 12.11.

F) Manufacture of the amine from the HCl-salt obtained by E).

1.80 gms. (0.0061 mol.) of HCl - salt obtained by E) were stirred for 25 minutes with a mixture of 8 mls. of 2 N ammonia and 50 mls. of water, followed by sucking off and washing with 50 mls. of water. The yield was 1.34 gms. The washing water after standing overnight yielded another 0.04 gms. Thus, altogether 1.38 gms. (0.0054 mol. or 89%) of the substance were obtained.

Analysis: Found: N 10.5; 10.8 $C_{16}H_{20}N_2O$ (256.34) calculated: N 10.93.

Example II

Manufacture of 3,4,5 - trimethoxy - benzoic ester from 3 - hydroxymethyl - 1,2,3,4, 6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine.

1.00 gm. (0.0039 mol.) of the alcohol obtained as described in Example I was added in 5 portions, while introducing nitrogen, to a solution of 4.0 gms. (0.017 mol.) of 3,4,5 - trimethoxy - benzoyl chloride in 35 mls. of absolute pyridine. Nitrogen was passed through for approximately a further half an hour until all the amine was dissolved, whereupon the solution was put aside at room temperature under nitrogen. On standing, a deposit was formed in the solution which had a slightly red colour. After 7 days, the pyridine was distilled off under nitrogen *in vacuo*. The residue was dissolved in 200 mls. of chloroform and the resulting red solution in chloroform was washed with a saturated Na_2CO_3 solution and water, and then acidified with 70% $HClO_4$. Next day a precipitate was sucked off and washed with much chloroform and subsequently with a little alcohol. The washed precipitate was introduced into water and made alkaline with 2 N ammonia. The resulting aqueous solution was extracted with chloroform and the extract obtained was washed with a little water. After drying over $MgSO_4$, the solvent was removed under vacuum. The residue could be crystallized from a little alcohol. Next day the precipitate was filtered off and washed with alcohol and ether. After crystallization from benzene-absolute alcohol, this yielded 1.19 gms. (0.0026 mol. or 67%) of the above-mentioned ester. After recrystallization from benzene the melting point, determined *in vacuo*, was 111° to 113° with decomposition.

Analysis: Found: C 68.5; 68.7; H 6.9, 6.8; N 6.1, 6.2 $C_{26}H_{30}N_2O_5$ (450.52) Calculated: C 69.31; H 6.71; N 6.22.

Example III

Manufacture of 3 - cyanomethyl - 1,2,3,4,6, 7,12,12b - octahydroindolo - (2,3 a) - quinolizine.

A solution of 2.40 gms. (0.059 mol.) of the *p* - toluene - sulphonic acid ester of 3 - hydroxymethyl - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine and 33 gms. (0.51 mol.) of KCN in 550 mls. of alcohol was boiled under reflux with stirring in an atmosphere of nitrogen for 6 hours. After cooling a solid substance resulting was filtered off and thoroughly washed with benzene, and the solvent was substantially removed by distillation *in vacuo*. The distillation process was interrupted several times for sucking off the resulting solid substance. After the alcohol was substantially distilled, another 200 mls. of benzene were added and the resulting solution was washed with a little water to remove the residual inorganic constituents. The benzene solution was concentrated *in vacuo* to 50 mls. After standing overnight a deposit was sucked off and washed with benzene and absolute alcohol. This yielded 0.78 gm. of solid material. Recrystallization from benzene yielded 0.64 gm. (0.0024 mol. or 41%) of the above-mentioned compound, melting point 218° to 219° (*in vacuo*). Working up the mother liquor yielded another 0.10 gm. (0.0004 mol. about 7%) of a little less pure cyano-compound (melting point determined *in vacuo*: 210° to 213°).

Analysis: Found: C 76.7; H 7.0; N 16.0 $C_{17}H_{19}N_3$ (265.37) Calculated: C 76.94; H 7.22; N. 15.84.

Example IV

Manufacture of 3 - ethoxycarbonyl - 1,2,3,4, 6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine.

A) Pyridine - 2.5 - dicarboxylic acid.

Into a three-neck 3 litre flask, provided with a stirrer, a thermometer, a long air-cooler and a drop funnel, the stem of which extended to the base of the flask, there were introduced 540 mls. of concentrated sulphuric acid (specific gravity 1.84) and, subsequently, 115 gms.

(0.95 mol.) of 5 - ethyl - 2 - methyl - pyridine, 20 gms. (0.18 mol.) of SeO_2 and 100 mls. of nitric acid (S.G.1.5). The mixture was carefully heated with stirring to a temperature of about 140°, at which a strong reaction set in. The heat was immediately removed from the flask and not resumed until the reaction had become less violent, the solution meanwhile having become black due to some separated selenium. At last, the solution was heated to 240° to 250° and at this temperature nitric acid (S.G.1.5) was slowly dripped in. The dripping process must not be too slow lest free selenium be formed in the solution, and not too rapid lest nitrous vapours escape through the cooler.

The oxidation was completed after 10 to 11 hours. This could be tested by examining a sample made strongly alkaline for the smell of 5 - ethyl - 2 - methyl - pyridine. In addition, when the reaction process is completed, the solution must no longer become black due to free selenium when the dripping of nitric acid is stopped.

In all about 300 mls. of the nitric acid were necessary for completing the oxidation.

Subsequently, the solution was cooled to about 170° and poured into 400 gms. of ice. After momentary boiling-up to remove nitrous vapours, the cooled solution was introduced into two gas-washing flasks each of 1 litre, provided with a sintered glass plate. SO_2 was introduced into these flasks for 5 hours in order to separate the selenium from the solution. The solution was then placed in a beaker and boiled for some time to render the selenium deposited more compact, and the hot solution then drawn off through a G4-glass filter. The filtrate was tested for the presence of SeO_3 by momentarily passing in SO_2. The clear solution obtained was diluted with 2 litres of water, and a solution of 500 gms. of NaOH in 500 mls. of water added dropwise. The solution, which had become warm, was cooled and pyridine - 2.5 - dicarboxylic acid having precipitated was sucked off. This must not be delayed too long (not more than about 3 hours), since otherwise sodium sulphate starts to crystallize.

The pyridine - 2.5 - dicarboxylic acid was washed with cold water and dried over KOH at 100°. The yield was 110 gms. (0.66 mol. or 68%) of pyridine - 2.5 - dicarboxylic acid, melting point 251° (decomp.)

B) Pyridine - 2.5 - dicarboxylic acid dimethyl ester.

110 gms. (0.66 mol.) of the compound obtained by A) was boiled with 1100 mls. of purified thionyl chloride on a water-bath for 12 hours. After filtration through a G4-glass filter in order to remove the small amount of non-dissolved substance, the thionyl chloride was removed by distillation at first at normal pressure and later under moderate reduced pressure, for example using a water-pump. The last residues of thionyl chloride were removed by standing the residue overnight under vacuum over KOH. The acid chloride, which had in the meantime solidified, was converted without further purification into the dimethylester by rapidly adding to it 400 mls. of absolute methanol dropwise. A vigorous reaction occurred, and after it had ceased the mixture was boiled under reflux for another few minutes. Subsequently, the mixture was poured into 2 litres of water while stirring and the methyl ester precipitated after cooling, was sucked off and washed with much cold water (about 800 mls.). After drying at 100° *in vacuo* above KOH, the yield was 113 gms. of the dimethylester. Recrystallization from methanol yielded 103 gms. (0.53 mol. or 80%) of pyridine 2.5 - dicarboxylic acid dimethyl ester with a melting point of 162° to 163°.

C) 2.5 - bis - carbomethoxy - piperidine.

30 gms. (0.15 mol.) of the compound obtained by B), 8 gms. of Raney - nickel W2 and 150 mls. of dioxane were introduced into a 1 litre autoclave. The ester was recrystallized from methanol with the addition of Raney-nickel (6 gms./litre) and the dioxane, after having been purified in the usual manner, was distilled from the Raney-nickel. After rinsing with hydrogen, a pressure of 145 atms. of hydrogen was provided, followed by slow heating of the autoclave while stirring. The absorption of hydrogen started at 60°. After another half an hour, during which the temperature rose further, the reduction was completed. The autoclave was then cooled down in cold water and opened. The catalyst was removed by filtration and the resulting solution evaporated to dryness under reduced pressure, using a water-pump. Vacuum distillation of the residue yielded:

1) 0.4 gm. with boiling point (0.4 mm.) 100° to 105°, n_D^{20} 1.4700

2) 166.8 gms. with boiling point (0.4 mm.) 105° to 130°, n_D^{20} 1.4775

3) 7.5 gms. with boiling point (0.4 mm.) 130° to 148°, n_D^{20} could not be determined.

Redistillation of fraction 2 yielded 13.0 gms. (0.065 mol. or 43%) of 2.5 - bis - carbomethoxy - piperidine with boiling point (0.4 mm.) 104° to 106°; n_D^{20} 1.4740.

D) γ - bromo - butyric acid ethyl ester.

81 gms. (1.0 mol.) of dry HBr were led into 86 gms. (1.0 mol.) of γ - butyrolactone on a boiling water-bath. After cooling, 119 gms. (1.0 mol.) of thionyl chloride were rapidly added dropwise. Subsequently, after further heating at 100° for a quarter of an hour, 50 gms. (1.1 mol.) of "super dry" ethanol were dripped into the cooled solution, followed by again heating at 100° for a quarter of an hour

and distillation *in vacuo*. The yield was:

1) 4.1 gms. with boiling point (14 mm.) up to 88°

2) 154 gms. (0.79 mol. or 79%) with boiling point (14 mm.) of 88°, n_D^{20} 1.4560 (lit.: n_D^{20} 1.4564).

E) γ - (2.5 - bis - carbomethoxypiperidino) - butyric acid ethyl ester.

25.0 gms. (0.12 mol.) of the substance obtained by C), 25.0 gms. (0.13 mol.) of γ - bromo - butyric acid ethyl ester and 17.5 gms. (0.12 mol.) of baked K_2CO_3 were heated while stirring in an atmosphere of nitrogen on a boiling water-bath for 27 hours. After cooling, 100 mls. of icy water were added, followed by extraction with ether. The resulting ethereal solution was dried over $MgSO_4$ and the residue obtained after distilling off the ether was distilled *in vacuo*. This yielded:

1) 0.5 gm. with boiling point (0.7 mm.) to 163°, n_D^{20} 1.4605

2) 31.5 gms. (0.10 mol. or 83%) with boiling point (0.7 mm.) of 163° to 165°, n_D^{20} 1.4689.

Analysis of fraction 2: found: C 57.1, 57.1; H 7.9, 7.9; N 4.4 $C_{15}H_{25}NO_6$ (315.38) calculated: C 57.12; H 7.99; N.4.44

F) 7 - carbethoxy - 1 - oxo - octahydroquinolizine.

4.0 gms. (0.17 gm-atom) of Na and 200 mls. of paraffin oil were introduced into a three-neck flask of 1 litre, whereafter the sodium was converted into NaH. A solution of 28.0 gms. (0.089 mol.) of the substance obtained by E) in 75 mls. of toluene was subsequently added dropwise, in an atmosphere of nitrogen during quarter of an hour, to the suspension of NaH which had cooled down to room temperature. The condensation was completed by boiling for another 5 hours under reflux. After cooling, the reaction mixture was decomposed by dripping in successively 10 mls. of ethanol and 10 mls. of water while cooling in ice and stirring. Subsequently, 200 mls. of concentrated hydrochloric acid were added and the reaction mixture was boiled under reflux until evolution of CO_2 had ceased, which was after from 4 to 6 hours. The mixture was then cooled and the aqueous layer separated from the paraffin - toluene layer which was washed once more with a little 2 N hydrochloric acid. The collected aqueous layer containing hydrochloric acid was washed several times with petroleum ether (40°—60°), and then evaporated to dryness *in vacuo*, stopping several times to filter off the deposited NaCl. The residue was subsequently boiled with a mixture consisting of 500 mls. of absolute ethanol, 200 mls. of benzene and 12 mls. of concentrated sulphuric acid for 4 hours. After distilling off 150 mls., the esterifying process was continued for another 3 hours, so that the surviving original carbomethoxy group is replaced now by a carbethoxy group. Then again 250 mls. were removed by distillation and, after cooling, the residue was poured into a mixture of 400 mls. of water and 400 gms. of ice. The solution was made alkaline with aqueous ammonia (10% NH_3, w/w) and then extracted with ether. The ethereal solution obtained was dried over $MgSO_4$ and then evaporated to dryness *in vacuo*, whereupon the residue was distilled *in vacuo*. The yield was:

1) 0.9 gm. with boiling point (0.5 mm.) of 110° to 112°, n_D^{20} 1.4846

2) 8.3 gms. with boiling point (0.5 mm.) of 112° to 114°, n_D^{20} 1.4873

3) 3.0 gms. with boiling point (0.5 mm.) of 114° to 126°, n_D^{20} 1.4878

Thus, in total 11.3 gms. (0.050 mol. or 56%) of 7 - carbethoxy - 1 - oxo - octahydroquinolizine were obtained as a pale yellow oil in which brown colouring occurred very soon in air, and which therefore had to be stored at −20° in an atmosphere of nitrogen.

Analysis of fraction 2: found: C 64.2, 64.1; H 8.9, 8.9; N 6.1 $C_{12}H_{19}NO_3$ (225.29) calculated: C 63.97; H 8.50; N 6.22

G) Phenylhydrazone of 7 - carbethoxy - 1 - oxo - octahydroquinolizine.

A mixture consisting of 3.60 gms. (0.016 mol.) of the substance obtained by F), 1.80 gms (0.017 mol.) of phenylhydrazine, 2.50 gms (0.042 mol.) of glacial acetic acid and 70 mls. of alcohol was boiled for 25 minutes in an atmosphere of nitrogen with reflux. The mixture was then cooled in ice and, after being supplemented with absolute ether up to a volume of 400 mls., 7.2 gms. of 70% $HClO_4$ were added. After standing in an ice-box for 3 hours, the $HClO_4$-salt of the phenylhydrazone was filtered off, washed with absolute ether and dried. This yielded 3.37 gms. (0.0081 mol. or 51%) of $HClO_4$-salt of the above-mentioned phenylhydrazone.

Analysis: found: N 9.8, 9.8 $C_{18}H_{26}ClN_3O_6$ (415.89) calculated: N 10.10

H) 3 - carbethoxy - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) quinolizine.

0.100 gm. (0.00024 mol.) of the substance obtained by G) was stored at room temperature under nitrogen with 3.0 mls. of alcohol saturated with dry HCl for 16 hours. Then 20 mls. of absolute ether were added and the resulting deposit was drawn off after standing for several hours. Treatment with 1 ml. of 1 N NH_4OH, sucking off, washing with water and drying, yielded 0.026 gm. (0.000087 mol. or 36%) of the above-mentioned compound with a melting point of 164° to 165°.

EXAMPLE V

3 - carbethoxy - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) - quinolozine.

If the 3 - carbethoxy - 1,2,3,4,6,7,12 -

hepta - hydroindolo (2,3 a) - quinolizinium - perchlorate, obtained as described in Example I D, is reduced with zinc and perchloric acid instead of $LiAlH_4$, as described in Example I E, the double bond in ring D is reduced selectively, the carbethoxy - group at the 3-position being retained.

2.5 mls. of 70% $HClO_4$ were added dropwise to a mixture consisting of 2.0 gms. (0.0050 mol.) of the compound obtained by the method of Example I D, 25 mls. of acetone, 25 mls. of tetrahydrofurane, 22 mls. of water and 2.5 gms. of zinc, followed by heating to 50° to 55° while stirring. The solution, which was initially yellow, was substantially decoloured after 65 minutes. Subsequently, the non-dissolved material was filtered off and the filtrate evaporated to dryness *in vacuo* at 30° to 40°, until 2 layers started to separate. The aqueous layer was decanted and the residual oil was washed with water twice. The oil was mixed with 2 mls. of alcohol and finally crystallized from 100 mls. of water. After the crystallization process was completed, the mother liquor was decanted and the crystallizate, after stirring with ether, was filtered off (1.4 gms.). Fractional crystallization from alcohol-benzene yielded 0.93 gm. (0.0023 mol. or 46%) of $HClO_4$-salt of 3 - carbethoxy - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,1 a) - quinolizine with melting point of 232° to 233°. With alkali the free base with a melting point of 164° to 165° was obtained therefrom. Analysis: found: C 72.5, 72.5; H 7.7, 7.7; N 9.2, 9.3 $C_{18}H_{22}N_2O_2$ (298.37) calculated: C 72.45; H 7.43; N 9.39

The infra-red absorption spectrum showed a C=O ester absorption at 1700 cm^{-1} and an NH absorption at 3390 cm^{-1}.

The compounds may be used not only as free bases, but also in the form of their salts, preferably as non-toxic acid-addition compounds, for example as their acid - addition salts with hydrochloric, citric or acetic acid.

For use in pharmaceutical preparations, they are worked up, for example, into tablets each of 225 mgms, which contain 50 mgms. of the active compound in addition to normal carriers such as lactose, saccharose, starch, talc and/or magnesium stearate.

For parenteral use there are manufactured, for example, injecting liquids containing from 10 to 50 mgms. of active substance according to the invention per millilitre of liquid and an amount of sodium chloride sufficient to make the solution isotonic with blood.

WHAT WE CLAIM IS:—

1. A substituted indoloquinolizine compound being a compound having the general Formula III set out in the accompanying drawings, or an acid - addition salt thereof wherein Y is a free, etherified or esterified hydroxyl group and $n^1=0$, 1 or 2, X is a free or esterified hydroxy group, a —C≡N group or a carboxyl group esterified by an aliphatic alcohol with 1 to 4 carbon atoms, and n=0—4.

2. 3 - carbethoxy - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine or an acid - addition salt thereof.

3. 3 - hydroxymethyl - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine or an acid-addition salt thereof.

4. The 3.4.5. - trimethoxy benzoic ester of 3 - hydroxymethyl - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine or an acid-addition salt thereof.

5. The 4 - methylbenzoic ester of 3 - hydroxymethyl - 1,2,3,4,6,7,12,12b - octahydroindolo - (2.3 a) - quinolizine or an acid-addition salt thereof.

6. 3 - cyanomethyl - 1,2,3,4,6,7,12,12b - octahydroindolo - (2,3 a) - quinolizine or an acid-addition salt thereof.

7. A process for preparing a compound as claimed in any one preceding claim which process comprises cyclizing a compound of the general Formula V in the accompanying drawings by means of a Dieckmann reaction in which formula X^1 represents X or an equivalent as herein defined, Y, n^1, X and n having the same significance as defined for Formula III in Claim 1, isolating the reaction product which has a keto group at the 2 - position and a $—CO(CH_2)_{n-1}—X^1$ group at the 3 - position, and converting the keto group at the 2 - position by reduction into a methylene group.

8. A process for preparing a compound as claimed in any one of Claims 1 to 6 which process comprises cyclizing a compound of the Formula VII in the accompanying drawings by means of a Bischler - Napieralsky reaction in which formula R_2 represents $—(CH_2)_n—X$ or an equivalent as herein defined, X, n, Y and n^1 having the same significance as defined for Formula III in Claim 1, and Z represents an anion of an inorganic acid, and reducing the compound of Formula VIII to form a compound corresponding to Formula III, or a compound which is converted into a compound of Formula III by conversion of the group R_2 into a group $—(CH_2)_n—X$ if it is not already such group.

9. A process for preparing a compound as claimed in any one of Claims 1 to 6 which process comprises reacting a compound of Formula XII in the accompanying drawings with a phenylhydrazine with or without substituents in the benzene ring, to form a compound corresponding to Formula XIII in which formulae R_2 represents $—(CH_2)_n—X$ or an equivalent as herein defined, X, Y, n and n^1 having the same significance as defined for Formula III in Claim 1, and $(Y)_{n1}$ being the substituents or substituents if any in the benzene ring of the phenylhydrazine, and cyclizing said compound of Formula XIII in a reaction known for a Fischer indole synthesis to form a compound of Formula III or a compound which is converted into a compound of Formula III by conversion of the group R_2 into

a $-(CH_2)_n-X$ group if it is not already such group.

10. A process for the manufacture of new substituted indoloquinolizine compounds or acid-addition salts thereof substantially as herein described with reference to any one of the foregoing specific Examples.

11. A substituted indoloquinolizine compound or a salt thereof when prepared by the process claimed in any one of Claims 7 to 10.

12. A pharmaceutical preparation containing as an active ingredient at least one compound as claimed in any of Claims 1 to 6 and 11 mixed with or dissolved or dispersed in a suitable solid or liquid carrier material.

13. A process for the manufacture of a pharmaceutical preparation, which process comprises mixing at least one compound as claimed in any of Claims 1 to 6 and 11 with, or dissolving or dispersing the same in, a suitable solid or liquid carrier material.

T. D. THREADGOLD,
Chartered Patent Agent,
Century House,
Shaftesbury Avenue,
London, W.C.2.
Agent for the Applicants.

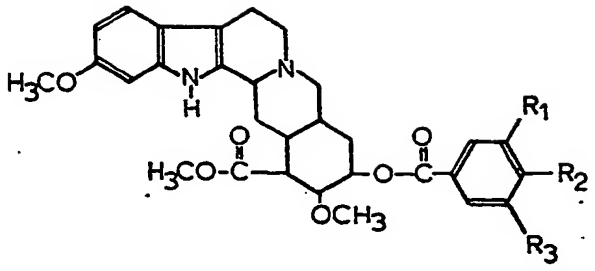
Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1965. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

983848 COMPLETE SPECIFICATION

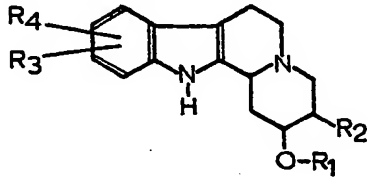
3 SHEETS *This drawing is a reproduction of the Original on a reduced scale*

Sheet 1

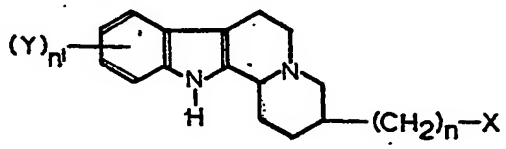
Formula I



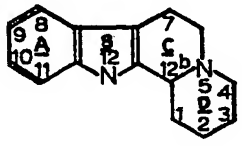
Formula II



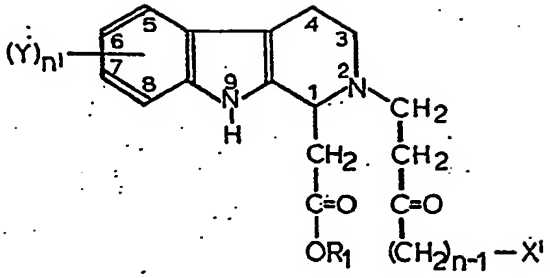
Formula III



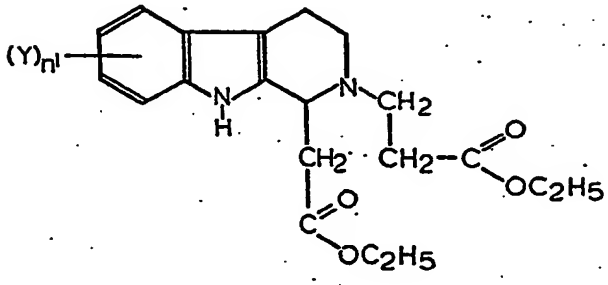
Formula IV



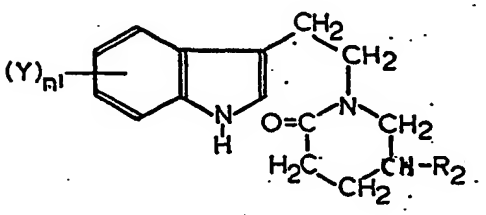
Formula V



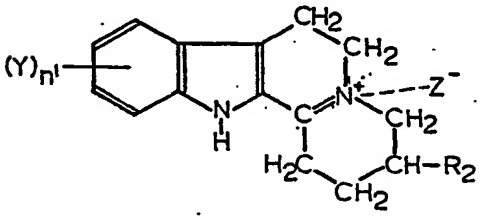
Formula VI



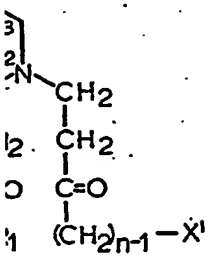
Formula VII

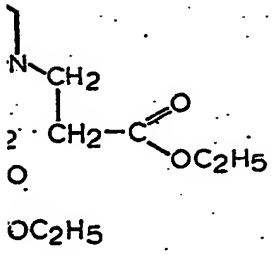


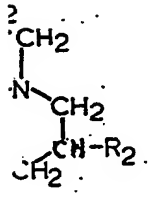
Formula VIII

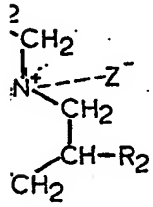


983848 COMPLETE SPECIFICATION
3 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheets 2 & 3

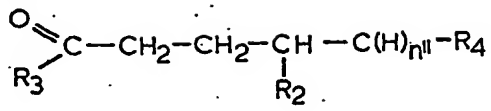




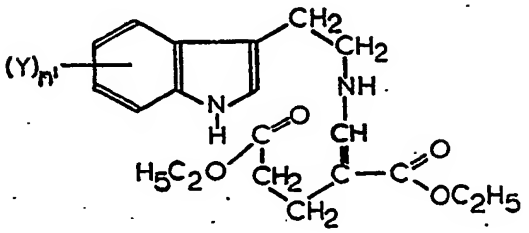




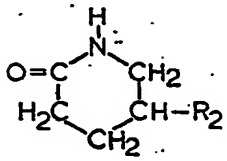
Formula IX



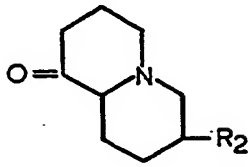
Formula X



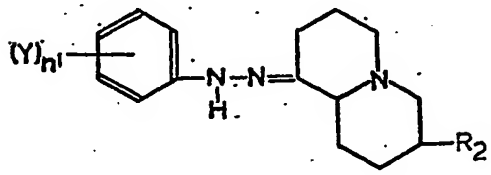
Formula XI



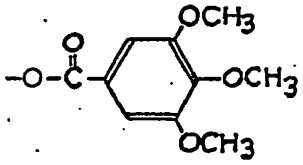
Formula XII



Formula XIII

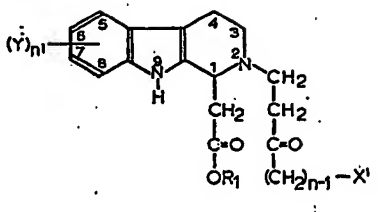


Formula XIV

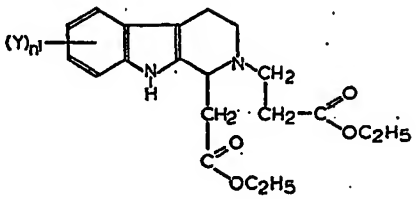


983848 COMPLETE SPECIFICATI
3 SHEETS This drawing is a reproducti the Original on a reduced : She & 3

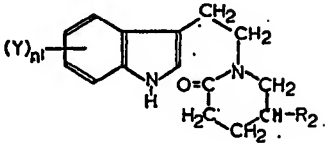
Formula V



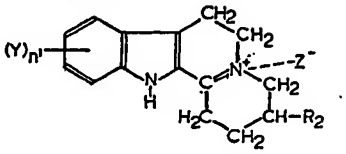
Formula VI



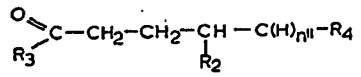
Formula VII



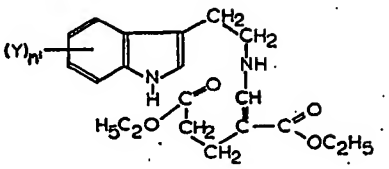
Formula VIII



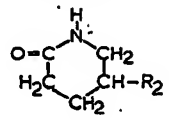
Formula IX



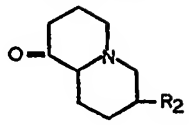
Formula X



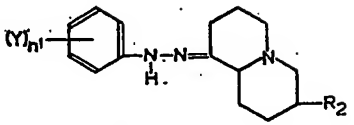
Formula XI



Formula XII



Formula XIII



Formula XIV